Pathologie Biologie 62 (2014) 233–240

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Cognitive impairment in obstructive sleep apnea

Troubles cognitifs dans l'apnée obstructive du sommeil

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A R T I C L E I N F O

Article history:
Received 26 November 2013
Accepted 13 May 2014
Available online 25 July 2014

Keywords:
Obstructive sleep apnea
Cognition
Neuropsychology
Continuous positive airway pressure
Electroencephalography
Neuroimaging
Aging

Mots clés :
Apnée obstructive du sommeil
Cognition
Neuropsychologie
Pression positive continue
Électroencéphalographie
Neuroimagerie
Vieillissement

A B S T R A C T

Obstructive sleep apnea (OSA) is characterised by repetitive cessation or reduction of airflow due to upper airway obstructions. These respiratory events lead to chronic sleep fragmentation and intermittent hypoxemia. Several studies have shown that OSA is associated with daytime sleepiness and cognitive dysfunctions, characterized by impairments of attention, episodic memory, working memory, and executive functions. This paper reviews the cognitive profile of adults with OSA and discusses the relative role of altered sleep and hypoxemia in the aetiology of these cognitive deficits. Markers of cognitive dysfunctions such as those measured with waking electroencephalography and neuroimaging are also presented. The effects of continuous positive airway pressure (CPAP) on cognitive functioning and the possibility of permanent brain damage associated with OSA are also discussed. Finally, this paper reviews the evidence suggesting that OSA is a risk factor for developing mild cognitive impairment and dementia in the aging population and stresses the importance of its early diagnosis and treatment.

R É S U M É

L'apnée obstructive du sommeil est caractérisée par des pauses respiratoires ou des réductions du débit aérien répétées qui sont dues à une obstruction des voies aériennes supérieures. Ces évènements respiratoires entraînent une fragmentation chronique du sommeil et une hypoxémie intermittente. Plusieurs études ont montré que l'apnée obstructive du sommeil est associée à la somnolence diurne ainsi qu'aux dysfonctions cognitives incluant des déficits au niveau de l'attention, de la mémoire épisodique, de la mémoire de travail et des fonctions exécutives. Cet article examine le profil cognitif observé chez les adultes présentant l'apnée obstructive du sommeil. Les rôles spécifiques de l'altération du sommeil et de l'hypoxémie dans l'étiologie des dysfonctions cognitive seront également abordés. Les marqueurs de dysfonctions cérébrales tels que ceux mesurés en électroencéphalographie et en neuroimagerie seront aussi présentés. Les études examinant l'efficacité du traitement par pression positive continue afin d'améliorer les déficits cognitifs dans cette population seront discutées ainsi que la possibilité que l'apnée obstructive du sommeil puisse causer des dommages permanents au cerveau. Enfin, cet article présente les récents résultats concernant la relation entre l'apnée obstructive du sommeil et le risque de développer un trouble cognitif léger et une démence dans la population âgée et souligne l'importance d'un diagnostic précoce en vue d'initier un traitement de l'apnée obstructive du sommeil.

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http://dx.doi.org/10.1016/j.patbio.2014.05.015
0369-8114/

1. Introduction

Obstructive sleep apnea (OSA) is a sleep disorder characterised by frequent breathing cessation and/or reduction of airflow due to partial or complete obstruction of the upper respiratory airways. These respiratory events occurring during sleep lead to intermittent hypoxemia and micro-arousals or awakenings. Sleep fragmentation is one of the leading causes of excessive daytime sleepiness, a predominant clinical manifestation of OSA. Daytime sleepiness in OSA is known to increase from two to seven times the risk of road accidents [1]. However, despite an increasing awareness of this health problem, 80% of individuals remain undiagnosed and untreated [2].

1.1. Night-time and daytime symptoms

Spouses or relatives sleeping in or near the bedroom of individuals presenting OSA usually report loud snoring that sometimes disturbs their own sleep. OSA patients report awaking breathless and choking during the night. In addition, they evaluate their sleep as non-restorative and report frequent awakenings overnight [3,4]. When waking up in the morning, subjects feel tired and may also have headaches and dry throat [3]. Most OSA patients complain of daytime sleepiness that usually occurs when performing tasks that require less attention (i.e. reading or watching television) [3,5]. With increasing OSA severity, sleepiness may occur while they drive, eat or work [3,5]. Most frequent cognitive complaints are a decrease in alertness, short-term memory problems, and lack of concentration [3,5]. However, our preliminary study recently showed a lack of insight in individuals with OSA with significantly more cognitive impairment [6]. Relatives and patients observe changes in their mood and personality, which includes irritability, depressed mood and anxiety. They often have sexual dysfunctions including loss of libido and impotence [3].

1.2. Diagnosis of obstructive sleep apnea

OSA is diagnosed through clinical history and polysomnography (PSG). Clinical history should include a complaint of excessive daytime sleepiness or two of the following symptoms: choking at night, recurrent awakenings, sensation of non-restorative sleep, and fatigue or inability to focus [5]. The PSG recording enables the confirmation of the OSA diagnosis. According to the recent update of American Academy of Sleep Medicine criteria, [7] obstructive apnea is a decrease greater than 90% of baseline airflow for at least 10 seconds, which is accompanied by a sustained or an increased respiratory effort. Obstructive hypopnea is a decrease greater than 30% of the airflow amplitude for at least 10 seconds accompanied with either a desaturation higher than 3% or an arousal. Frequency of respiratory events is measured by the apnea-hypopnea index (AHI) obtained by summing the respiratory events and dividing by the number of hours of sleep. Recommended criteria for the diagnosis of OSA are an AHI higher than 5 for young and middle-aged adults while criteria of AHI higher than 20 was suggested for the elderly [8,9]. OSA severity depends on the presence and intensity of daytime sleepiness and the frequency of respiratory events. The assessment of the severity of sleepiness relies on the type of task during which the episode occurs (i.e. reading vs. driving) and the impact of sleepiness on the social and functional aspects of life. The assessment of severity of respiratory events includes three levels in young and middle-aged adults: mild OSA (AHI between 5 and 15), moderate OSA (AHI between 15 and 30) and severe OSA (AHI higher than 30) [5].

1.3. Epidemiology

Epidemiological findings vary according to age, sex and apnea severity. When a criterion of an AHI $\geq$ 15 is used, the prevalence is estimated at 2 to 14% in middle-aged adults (39-59 years), but shows an increase to 20% in those aged 60 to 95 years. Some authors suppose that the increase in prevalence with age is due to anatomical changes in the upper respiratory airways or the coexistence of a medical disorder [10]. Others explain that OSA is more prevalent in elderly than in middle-aged individuals because OSA cases accumulate from a constant incident rate [2]. Moreover, the prevalence is twice as high among men (25%) than women (11%). Finally, in a population aged between 39 and 99 years old, mild OSA is more prevalent (29%) than moderate to severe OSA (18%) [2].

1.4. Pathophysiology

Partial or complete obstructions of the upper airway are due to the relaxation of the throat muscles and tongue, which collapse the airways during sleep. Airway obstructions create intermittent hypoxemia and hypercapnia. Peripheral (aortic) and central (medulla oblongata) chemoreceptors both stimulate respiratory centers to increase ventilation since they are sensitive to hypoxemia and hypercapnia. The end of respiratory events usually occurs through the occurrence of awakening or arousal and is associated with sympathetic activation [11]. OSA also creates inflammation and endothelial dysfunction, which reduce vascular elasticity and increase coagulation. Altogether, these factors predispose to atherosclerosis [11]. The combination of reduced oxygenation reaching tissues and vascular damages can lead to cellular dysfunctions in several organs such as the heart and the brain.

1.5. Risk factors and comorbidities

Overweight, obesity, central body fat distribution and large neck girth have been identified as important risk factors for OSA [12]. Morphological factors such as dimorphisms related to the size or position of the mandible or maxilla, narrow nasal cavity, a low soft palate, and enlarged tonsils also play an important role in the development of OSA [12]. Other factors may contribute to the risk of OSA, including hormonal changes, alcohol consumption, smoking and nasal congestion, but their causal role is not well established. Hypertension, diabetes, coronary heart disease, myocardial infarction, congestive heart failure and stroke were found to be associated with OSA. The emergence of these comorbid conditions may be due, in part, to common risk factors (i.e. obesity and hypertension), but OSA may also have a causal role in these diseases since hypoxemia and hypercapnia can lead to vascular dysfunctions [13]. Genetically, it has been reported that the isoform E4 from the *ApoE* gene, identified as a risk factor for Alzheimer disease, is more frequently found in OSA patients than in healthy control individuals, [14,15] but a meta-analysis based on published literature failed to support this association between ApoE4 and OSA [16].

1.6. Continuous positive airway pressure treatment

Continuous positive airway pressure (CPAP) improves overall OSA symptoms by keeping the upper airways open using air pressure, which consequently decreases hypoxemia and sleep fragmentation [17]. CPAP treatment globally improves subjective daytime functioning and performance in cognitive tests (see details in the following sections) [18–24]. In addition, CPAP treatment normalizes electroencephalographic (EEG) recordings performed during the waking state among OSA subjects and this normalization in EEG is associated with decreased daytime sleepiness [25,26]. However, CPAP should be used for at least four hours per night for a subjective effect on sleepiness, and a minimum of six hours per night for an effect on objectively measured sleepiness [27].

2. Cognitive impairment in OSA

Several studies have investigated the cognitive profile of OSA patients and recently, a meta-review analysed neurocognitive functions in OSA based on systematic reviews and meta-analyses [28]. Published studies have identified attention, episodic memory, working memory, and executive functions as the most affected cognitive domains in OSA, [22,29–37] whereas most aspects of language are preserved in this population [22,29,38–45] and heterogeneous results are found for psychomotor speed [46]. In the following section, cognitive deficits observed in OSA for each cognitive domain are described. Table 1 presents an overview of cognitive domains affected in OSA, neuropsychological tests generally used and the efficiency of CPAP to improve each cognitive function.

2.1. Attention

Attention is generally divided into sustained, selective and divided attention. Sustained attention, which also refers to vigilance in the present paper, is a mechanism that involves alertness and receptivity to stimuli for a continuing time period; selective attention enables to treat or ignore stimuli according to their relevance; and divided attention allows multiple tasks to be executed simultaneously [40]. Several studies have demonstrated that OSA subjects show impairments for all three attention components [29,39,41] and these observations were confirmed by a meta-review [28]. When compared to healthy controls, OSA subjects have more lapses and/or longer reaction times in tasks requiring sustained attention, selective attention, or vigilance [30,32,41,43–45]. In conditions requiring divided attention, such as driving in a simulator while performing another cognitive task, individuals with OSA showed an increase in reaction times and "off road" events compared to controls [41]. Thus, the efficient allocation of attentional resources to multiple relevant stimuli has proven difficult in individuals with OSA. Given the severity and the extent of attention deficits, it has been suggested that vigilance and attention deficits could influence other aspects of cognitive deficits attributed to OSA [36,37,41]. According to this hypothesis, attention deficits probably worsen other cognitive deficits that are secondary to OSA, such as executive functions and episodic memory impairments.

A review of cognitive changes associated with CPAP treatment reported that 11 of the 17 studies showed a significant improvement in vigilance and attention with CPAP [47]. It was also observed that as few as 15 days of CPAP treatment was sufficient to obtain significant improvement in sustained attention tests [22]. However, despite significantly improving attention, CPAP is often unable to fully normalize attention processes in OSA. In fact, according to a study by Lau et al. (2010), selective and divided attention deficits were still observed after three months of CPAP treatment when compared to control subjects [23]. These results suggest that attention deficits in OSA are partially caused by sleep fragmentation and hypoxemia, but that OSA probably causes permanent damage to regions of the brain involved in attention processes [22,23,29].

2.2. Executive functions

Executive functions are a complex concept that comprises many cognitive skills including behavioural inhibition, mental flexibility, working memory, fluid reasoning, and problem solving. They allow individuals to adaptively use their basic skills (e.g. language, visuo-perceptual, memory) to perform adequately in a changing environment [38]. A recent meta-analysis reported that executive functions are impaired in OSA for all five sub-domains studied, namely: inhibition, shifting, updating/monitoring information in working memory, generating new information and fluid reasoning and problem solving [42]. Inhibition, which refers to the capacity to stop an automatic or ongoing response to an event, [49] is required in cognitive tests such as Stroop (inhibition condition) or Go No-Go tasks. In these tasks, OSA subjects make significantly more mistakes or have increased reaction times compared to controls [50]. Moderate to severe OSA subjects also made more impulsive errors on maze completion [30].

Shifting, or mental flexibility, is the ability to move from one cognitive or behavioural strategy to another. In the Wisconsin Card Sorting Tests, subjects with OSA showed an increased number of perseverative responses when compared to control subjects [50,51]. Reduced mental flexibility was also documented in studies using the Trail making test B and the computerized Zimmermann-Fimm Tests battery for Attentional Performance, where OSA subjects required more time to complete the tasks than controls [30,50,51].

Working memory refers to the ability to retain, manipulate, update and monitor information for the duration of a task. The concept of working memory encompasses the central executive, which enables information manipulation by subsystems [52]. For example, the ability to mentally reverse a digit string or visual

Table 1
Cognitive impairment in OSA and neuropsychological assessment.

Cognitive domains Impaired in OSA	Improvement following CPAP	Neuropsychological tests typically used
Attention		
Sustained	Yes	Four choice reaction time test [27,30]; **Continuous Performance test* [39,42]; Psychomotor vigilance task [41]; **Trail making test A* [30,42]; Cancellation task [27]; Simon and Flanker task [43]; Driving simulation [39]
Selective	No	
Divided	No	
Executive functions		
Behavioral inhibition	Incongruent results	**Stroop* [46]; **Maze* [27]; **Wisconsin card sorting test* [46,47]; **Trail making test B* [19,46,47]; Zimmerman-Fimm tests battery for attentional performance [34]; Verbal fluency [19,20,46]; **Digit Span (backward)* [46,47]; Tower of Toronto [46]
Flexibility	Yes	
Working memory	No	
Planning and problem solving	Incongruent results	
Motor function		
Psychomotor speed and fine coordination	No	**Purdue pegboard test* [19,24,46]
Episodic memory		
Immediate recall	Yes	**Rey Auditory-Verbal learning test* [48]; **WMS logical stories* [48]; California verbal learning test [48]; Buschke SRT [48]; WMS figural recall [48]; Brief Visuospatial Memory Test revised [48]
Learning	Yes	
Delayed recall	Yes	
Recognition memory	Incongruent results	

* Tests from the neuropsychological test battery proposed by Décary et al. (2000) [31].

sequences to repeat it backward reflects a working memory capacity. Studies using the Digit backward test showed that OSA subjects perform poorly on this working memory task compared to controls [50,51]. Saunamaki and Jehkonen (2007) also found that working memory was among the most frequently impaired components of the executive functions in this population [48]. However, more studies investigating working memory among OSA patients are needed to confirm these observations.

Problem solving, which involve the evaluation and selection of a sequence of actions in order to achieve a goal [40], was found to be impaired in individuals with OSA. In fact, in a task that is typically used to assess this component of executive functions, namely the Tower Tasks, one study showed that OSA subjects need a higher number of steps before solving problems [50]. Some executive aspects of verbal behaviour, such as mental processing speed, flexibility and synthetic skills are also diminished in adults with OSA, despite otherwise normal language skills [22,30,50].

In sum, studies have found deficits in most aspects of executive functioning in OSA, characterised by decreased processing speed, increased perseverative responses or behaviours, impulsivity, and difficulty with problems solving. However, it is important to mention the high level of heterogeneity in the results found among studies that could be partly due to population heterogeneity (including premorbid intellectual functioning and education), various disease severities and the large number of executive function tasks [42].

Both a recent meta-analysis and a review showed that CPAP treatments induce a small to moderate improvement in executive functions [42,53]. For example, a study found an improvement of mental flexibility (Trail B) and verbal fluency (semantic) in OSA after a short CPAP treatment (15 days). Long treatments (four months) did not result in any further improvement on executive cognitive tests [22]. Behavioural inhibition and working memory were not improved following a short (15 days) and a long (four months) CPAP treatments when compared to pre-treatment condition [22]. Moreover, it was reported that mental flexibility of OSA subjects did not reach the level of control subjects after a three-month treatment [23]. Taken together, these studies suggest that only certain aspect of executive functions improve after a short CPAP treatment while not systematically reaching the level of controls performance [21–23]. The fact that other cognitive functions, such as attention and vigilance, are necessary to perform most executive function tasks, and that OSA may cause permanent damage to the prefrontal cortex [39] could explain part of the variability in studies investigating the effects of CPAP on this cognitive domain.

2.3. Psychomotor speed and fine coordination

Tests involving psychomotor speed and fine coordination are generally used to investigate motor dysfunctions that occur in the context of intact capacity for normal movement. In individuals with OSA, reduction of manual dexterity was reported on Purdue Pegboard Test [21,30,50] and fine motor coordination was found to be more sensitive to chronic hypoxemia than sleep fragmentation [29]. A recent literature review showed that half of the published studies reported that patients with OSA have a reduced information processing speed compared to control subjects [46]. This reduced information processing probably impacts performances in several cognitive tasks such as those evaluating executive functions (i.e. Tower tasks or Trail B) and visual attention. It is not surprising that OSA patients performed worse than healthy control subjects on all timed tests that included a visuomotor coordination component [47].

Contrary to other cognitive domains, psychomotor speed and fine coordination are not significantly improved with CPAP treatments, which suggests that OSA may cause permanent damages to cortical and subcortical areas involved in motor skills [17,26,46].

2.4. Episodic memory

Episodic memory was extensively studied among OSA subjects and refers to the memorization of verbal or visual information in a spatio-temporal context [54]. Episodic memory tasks generally include immediate recall, total recall over multiple trials or learnings, delayed recall, and recognition memory. Learning and recall of list of words, such as in the Rey Auditory-Verbal Learning Tests and the California Verbal Learning Tests, are examples of episodic memory tests. A recent meta-analysis showed that OSA patients have different patterns of deficits for verbal and visual episodic memory. Indeed, for verbal material, each memory component, namely immediate and delayed recall, learning and recognition, was impaired in OSA patients when compared to controls [55]. However, in visuospatial episodic memory tasks, OSA patients showed impairment only for immediate and delayed recalls, and had normal results for learning slope and recognition [55,56]. It was suggested that this impairment was not entirely accounted for by a reduction of attention or by OSA severity [57].

A review on the effect of CPAP treatments reported an improvement in memory in about half of the studies [47]. Although all components of verbal episodic memory evaluation are affected in OSA [55], a three-month CPAP treatment resulted in normalisation of performances for immediate and delayed memory, and for both verbal and visuospatial learning [22,23].

2.5. Role of sleep characteristics and hypoxemia in cognitive deficits observed in OSA

OSA causes sleep disruption, which leads to changes in sleep architecture and excessive daytime sleepiness. Intermittent hypoxemia is also a major consequence of OSA. Several studies have aimed to understand the specific role of altered sleep quality/quantity and hypoxemia in the aetiology of cognitive dysfunctions in this population.

2.5.1. Sleep architecture and sleep fragmentation

Sleep fragmentation is the most systematically studied sleep variable in association with cognition among this population. According to a critical review and a recent meta-review, the more severe is sleep fragmentation, the more impaired are the performance on attention and vigilance tests [26,28]. Learning and memory also seem affected by sleep fragmentation in OSA patients. In fact, in a study by Djonlagic et al. (2014), the authors investigated the sleep-dependent memory consolidation in 20 OSA patients and 20 control subjects. They found that OSA patients had less overnight improvement on the motor sequence learning task when compared to control subjects. More specifically, sleep fragmentation predicted overnight improvement on the motor sequence learning task [58].

Sleep architecture and more specifically the percentage of each sleep stages may have an impact on daytime cognitive functioning in the OSA population, since most PSG studies found small but significant changes in sleep architecture. In fact, most PSG studies documented an increased percentage of stage 1 sleep, as well as elevated arousal and micro-arousal indexes, while no change for total sleep time was generally observed. In contrast, a majority of studies found a decrease in the percentages of stages 3-4 sleep and rapid eye movement (REM) sleep [43,59]. However, an association between changes in the percentage of each sleep stage and the cognitive profile of OSA subjects has not been documented in the literature. Considering that loss of non-rapid eye movement (NREM) and REM sleep is known to be associated with decreased

performance in tasks involving episodic memory in healthy individuals [60], changes in sleep architecture associated with OSA may independently contribute to their cognitive deficits, but this hypothesis needs to be tested.

Studies evaluating the effect of excessive daytime sleepiness on cognitive deficits in OSA found that sleepiness can only partially account for cognitive deficits [41,43,61,62]. Indeed, studies on the effect of CPAP treatment on cognition reported a global improvement of cognitive functions [33,48,56–59]. However, CPAP treatment fails to improve fine motor coordination and some subjects still have memory and executive dysfunctions after treatment [21,23,24,29]. This suggests that history of hypoxia and/or chronic sleep fragmentation may cause some permanent damage to cortical and subcortical structures and that sleepiness cannot explain all cognitive impairments. In parallel, it is important to note that comorbidities associated with OSA such as obesity, diabetes, and hypertension have recently been identified as factors that contribute independently to sleep fragmentation and cognitive deficits in OSA [63].

2.5.2. Hypoxemia

Animals and brain imaging studies have found that OSA, and more specifically hypoxemia, causes neuronal damage in multiple brain regions [39,64]. Hypoxemia followed by re-oxygenation results in similar changes as those observed in an ischemic/reperfusion injury [65]. This type of injury increases free radicals and inflammation, which are particularly damaging for endothelial and neuronal integrity, especially in the hippocampus and the frontal cortex [65,66]. Furthermore, endothelial dysfunction, caused by OSA, increases blood pressure and coagulation that both predispose and increase risk of silent stroke in OSA [11].

Large population studies have confirmed a small, but significant association between hypoxemia and some cognitive deficits, including attention impairments, slow processing speed and executive dysfunctions [39,50,61]. The heterogeneity found in the literature for the association between hypoxemia and cognitive functioning is possibly due to the role of non-controlled variables, such as age or premorbid intellectual functioning. Animal models have shown that intermittent hypoxemia was associated with impairments in the execution component of attention (i.e. set-shifting) and to a particular vulnerability to neuronal loss in the frontal lobe [67,68].

2.6. Risk factors for cognitive impairment in OSA

Several studies investigated the association between the severity of OSA as measured with AIH and the cognitive deficits found in this population. Heterogeneous results were found with some studies showing that adults with severe OSA (AHI $\geq$ 30) are more likely to present cognitive deficits than those with mild or moderate OSA, [69] while other studies found no association [42–44,61,70]. One problem that may limit the interpretation of this lack of association is that there is currently insufficient data for mild to moderate OSA, since most studies only included moderate and severe OSA patients [42].

Age was also found to be associated with greater cognitive dysfunctions, where middle-aged adults with severe OSA are more at risk of cognitive deficits than younger adults with the same OSA severity [71]. A study comparing young and older OSA subjects showed Group (i.e. OSA versus control) and age effects on several cognitive tests, suggesting that both OSA and age contribute to cognitive dysfunctions in older individuals with OSA [33].

Premorbid cognitive functioning, or cognitive reserve, seems to have a protective effect on cognitive deterioration in OSA. In fact, OSA subjects with higher intelligence have similar performance on attention/alertness tasks when compared to healthy controls with equivalent intelligence. In contrast, OSA subjects with lower intelligence have lower performance on attention tests compared to controls with similar intelligence [72]. Future studies should include premorbid intelligence or cognitive reserve when evaluating the impact of OSA on cognitive functioning.

Several comorbidities associated with OSA, such as obesity, hypertension, diabetes, congestive heart failure and cerebrovascular accidents, known to be independently associated with cognitive deficits, may worsen neurocognitive function in subjects with OSA [63,65].

It was reported that ApoE4 allele carriers among OSA subjects had a lower performance on spatial working memory tasks when compared to non-carrier OSA subjects while this genetic effect on cognition was not observed in controls [73]. In parallel, a recent study found a poorer performance on cognitive tests requiring memory and executive functions in ApoE4 carriers with a moderate-severe OSA (AHI $\geq$ 15) than what it was observed in ApoE4 carriers without OSA [74]. These results suggest that OSA and genetic interaction leads to greater risk of cognitive dysfunctions.

3. Electroencephalography and event-related potentials

Spectral analysis of the waking EEG allows evaluating the content of the EEG signal and is recognised as an index of cerebral functioning. Several studies found an EEG slowing across all scalp regions in OSA subjects when compared to controls [75,26,76]. More specifically, an increase in the relative theta and delta powers in parietal, temporal and occipital regions was reported in patients with severe OSA when compared to control subjects [77]. EEG slowing was associated with a disruption of sustained attention on cognitive tests, which results in increasing omission and reaction times during a task [75]. It has been observed that more EEG slowing was associated with more time spent with oxygen saturation under 90% [76]. An improvement of EEG slowing across all scalp regions was found following a CPAP treatment and was linked to an improvement in cognitive functions and daytime sleepiness [26,78]. When moderate to severe OSA were compared to control subjects before and after six months of CPAP treatments, quantitative waking EEG showed an increase of relative delta power in all cortical regions for both before and after CPAP, [77] suggesting that some damages due to OSA may permanently alter brain function.

Event-related potential (ERP) recordings during an attention task are a widely used method to assess cerebral dysfunction and attention deficits [79]. A recent review on ERP abnormalities in OSA highlighted the increased P300 latency in visual and auditory tasks observed in this population [80]. The P300 component is associated with the occurrence of a target stimulus and represents classification speed (latency) and attention resources allocated to the task (amplitude) [81,82]. A recent study evaluating the association between ERP abnormality and EEG slowing found that the late portion of the P300 was associated with an increase in theta power in OSA, but this correlation was not found in control subjects. Considering that an increase in theta power at rest generally reflects a general vigilance decrement, this result suggests that attention deficits are associated with decreased vigilance in OSA. In this study, lower P3a amplitude was correlated with a decrease in beta 1 spectral power in OSA patients [83]. However, contrary to the P300, P3a amplitude was not correlated with slow EEG frequencies, which suggests that P3a anomalies were not caused by a general vigilance decrement during the attention task in this population. Others studies investigated ERP components that reflect automatic and volitional orientation of attention towards relevant and irrelevant stimuli and showed

abnormalities in most ERP components in OSA subjects compared to control subjects [84,85]. In a review by Raggi and Ferri (2010), it was also shown that P300 amplitude correlated with higher respiratory event index [80]. Heterogeneous results were found for the efficiency of CPAP to restore ERP: some studies showed an improvement in P300 latency after CPAP treatment, [86,87] but other studies did not find any improvement [88,89]. Interestingly, one study found that abnormalities observed in P300 were irreversible, but only in the elderly [90].

4. Neuroimaging findings

Studies using different brain imaging techniques investigated neuroanatomical changes and cerebral functioning to identify the consequences of OSA on the brain, and to understand the causes of cognitive impairments in this population.

Structural brain imaging studies using magnetic resonance imaging (MRI) combined with voxel-based morphometry showed reduced grey matter density in subjects with OSA on overall volume and in distinct brain regions, namely the parietal, frontal and temporal lobes; the hippocampus, the amygdala, the anterior cingulate, the caudate nucleus and the cerebellum (See Ferini-Strambi 2013 for a review [91]). Studies showed positive correlations between changes in grey matter density in the hippocampus, caudate nucleus and frontal regions, and cognitive alterations in episodic memory, attention and executive functions [66,92].

More recently, diffusion tensor imaging was used to characterize white matter in OSA patients. A wide range of white matter structures, including medullary, cerebellar, basal ganglia, prefrontal and frontal, limbic, insular, cingulum bundle, external capsule, corpus callosum, temporal, occipital, and corona radiata regions, was shown to be affected [93,94]. The structures showing white matter abnormalities could be associated with specific cognitive deficits and altered mood in subjects with OSA, but further studies are needed to confirm this hypothesis.

Several functional neuroimaging studies reported changes in blood flow and resting metabolism function in patients with OSA. Positron emission tomography, single-photon emission computed spectroscopy and magnetic resonance spectroscopy studies all reported multiple regions of hypoperfusion or hypometabolism, more specifically in the prefrontal cortex, the parieto-temporal junction, the precuneus, the cuneus, the cingulate cortex, and the hippocampal regions. (See Ferini-Strambi 2013 for a review) [91].

One recent study measuring resting brain activity with functional MRI reported that cognitive and sensorimotor brain networks (i.e. medial prefrontal cortex, dorsolateral prefrontal cortex and precentral gyrus) showed a decrease in resting-state functional connectivity, whereas right posterior cingulate cortex showed an increase of resting-state functional connectivity that possibly reflected compensation [59]. According to this study, auditory and visual networks remained unchanged in this population and abnormal functional connectivity was not due to sleepiness, but was rather associated with loss of grey matter density.

Other functional MRI studies investigated patterns of activations and deactivations while OSA subjects performed various cognitive tasks. Among the most interesting studies is the one by Thomas et al. (2005), where OSA subjects showed decreased dorsolateral prefrontal cortex activation during a memory task, and this change in cerebral activation was associated with poorer behavioural performances compared to controls [95]. Interestingly, in another study using a working memory task, OSA subjects performed similarly to control subjects, but showed an activation of supplementary brain structures, which may represent compensatory mechanisms [96]. The presence of such compensatory mechanisms was also suggested in a study using a verbal learning task, in which OSA subjects showed activation in additional brain regions, more specifically in the frontal lobes, the cingulate gyrus and the parieto-temporal junction, compared to control subjects [97]. In this specific study, the compensatory hypothesis was supported by the fact that after a CPAP treatment, OSA subjects showed decreased activations in those additional brain regions during a verbal learning task.

5. Cognition in elderly with OSA

OSA is considered as a risk factor for cognitive decline in the elderly. In a prospective study performed in 298 women aged 82 years old, 44,8% of women with sleep-disordered breathing (AHI $\geq$ 15) developed mild cognitive impairment (MCI) or dementia after a five-year follow-up, compared to 31,1% of women without sleep-disordered breathing [98]. After adjustments for age, race, body mass index, education level, smoking, diabetes, hypertension and medication use, the presence of sleep-disordered breathing was still associated with greater risk of developing subsequent mild cognitive impairment or dementia (odd ratio: 1.85; 95% confidence interval, 1.11-3.08). The authors also found that more severe hypoxemia was associated with a higher incidence of mild cognitive impairment or dementia. According to preliminary results from our laboratory, the percentage of OSA subjects presenting MCI is higher than 30% [70], which is significantly greater than the proportion of MCI generally observed among control subjects without OSA.

A randomised double-blind placebo-controlled trial examined the effect of CPAP treatment to improve cognitive functioning among subjects with mild to moderate Alzheimer's disease with concomitant OSA [8]. Participants were separated into therapeutic group with CPAP for six weeks or placebo CPAP group for three weeks, followed by a CPAP treatment of three weeks. Comparison between pre- and post-treatment after three weeks in both groups showed mild but significant improvement of neuropsychological tests scores, more specifically for episodic verbal learning, memory, cognitive flexibility and mental processing speed [8].

OSA is a major public health problem, which often goes undiagnosed and untreated. OSA symptoms in older adults are often attributed to the normal processes of aging. Thus, it is important for practitioners to investigate for the presence of OSA in order to increase OSA diagnosis and minimize negative consequences of OSA on the brain.

6. Future research directions

Very few studies were performed among older OSA patients. Consequently, the impact of OSA on cognitive functioning in elderly is not clear. Undiagnosed and untreated OSA in the aging population may increase the likelihood of cognitive deficits in this population, and can increase the risk of dementia. Premorbid intelligence, education or cognitive reserve is probably a significant variable that interacts with OSA severity in cognitive deficit manifestation. Future studies should add these variables in order to understand their role on how OSA alters brain functioning.

Moreover, to date, most studies included moderate and severe OSA patients, while mild OSA are generally excluded. This focus on more severe AHI prevents understanding the impact of mild OSA on cognitive and brain dysfunctions. Finally, the role of genetics and more specifically the ApoE4 should be investigated in larger samples.

Disclosure of interest

Katia Gagnon, Andrée-Ann Baril, Maxime Fortin, Anne Décary, and Nadia Gosselin: none of these authors has a financial interest or other potential conflict of interest.

Jean-François Gagnon received a research grant from W. Garfield Weston Foundation for a research program that is not related to this review.

Chantal Lafond received honoraria for polysomnographic investigation from Biron-Soins du sommeil.

Alex Desautels received research grants from Novartis and GlaxoSmithKline. He received honoraria for speaking engagements from UCB and Paladin Labs. These activities are not relevant to the particular topic of this manuscript.

Jacques Montplaisir received research grants/support from Merck, GlaxoSmithKline, W. Garfield Weston Foundation. Dr. Montplaisir served as an advisor for Merck, Servier, Valeant Pharmaceutical, Impax Laboratories, Jazz Pharmaceutical, and Sanofi Aventis. He received honoraria for speaking engagements from Valeant Pharmaceutical, Otsuka Pharmaceutical. These activities are not relevant to the particular topic of this manuscript.

References

[1] Strohl KP, Brown DB, Collop N, George CF, Grunstein RR, Han F, et al. An official American thoracic society clinical practice guideline: Sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. Am J Respir Crit Care Med 2013;187:1259–66.
[2] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population Health Perspective. Am J Respir Crit Care Med 2002;165:1217–39.
[3] American Academy of Sleep Medicine, Hauri PJ. The international classification of sleep disorders: diagnostic and coding manual, Second edition, Westchester, IL: American Academy of Sleep Medicine; 2005.
[4] Meyers KA, Mrkobrada M, Simel DS. Does this patient have obstructive sleep apnea? The rational clinical examination systematic review. JAMA 2013;310:731–41.
[5] American Academy of Sleep Medicine Task Force. Sleep–related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667–89.
[6] Fortin M, Gagnon K, Baril AA, D'Aragon C, Gagnon JF, Gosselin N. Are cognitive deficits observed in obstructive sleep apnea associated with cognitive complaints? [abstract]In: World Association of Sleep Medicine Congress. 2013. p. 145 [Available from: URL: http://www.wasmcongress.com/wp-content/uploads/2012/03/WASM-2013-Abstracts-Publication.pdf].
[7] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manuel for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597–619.
[8] Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, et al. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J Am Geriatr Soc 2008;56:2076–81.
[9] Cooke JR, Ancoli-Israel S, Liu L, Loredo JS, Natarajan L, Palmer BS, et al. Continuous positive airway pressure deepens sleep in patients with Alzheimer's disease and obstructive sleep apnea. Sleep Med 2009;10:1101–6.
[10] Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lo YL, et al. The influence of aging on pharyngeal collapsibility during sleep. Chest 2007;131:1702–9.
[11] Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. Chest 2008;133: 793–804.
[12] Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA 2004;291:2013–6.
[13] Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290:1906–14.
[14] Kadotani H, Kadotani T, Young T, Peppard PE, Finn L, Colrain IM, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. JAMA 2001;285:2888–90.
[15] Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. Neurology 2004;63:664–8.
[16] Thakre TP, Mamtani MR, Kulkami H. Lack of association of the ApoE4 allele with the risk of obstructive sleep apnea: meta-analysis and meta-regression. Sleep 2009;32:1507–11.
[17] Loredo JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure vs placebo continuous positive airway pressure on sleep quality in obstructive sleep apnea. Chest 1999;116:1545–9.
[18] Montserrat JM, Ferrer M, Hernandez L, Farré R, Vilagut G, Navajas D, et al. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome. Am J Respir Crit Care Med 2001;164:608–13.
[19] Muñoz A, Mayoralas LR, Barbé F, Pericas J, Agusti AG. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. Eur Respir J 2000;15:676–81.
[20] Bardwell WA, Ancoli-Israel S, Berry CC, Dismsdale JE. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: a placebo-controlled study. Psychosom Med 2001;63:579–84.
[21] Bédard MA, Montplaisir J, Malo J, Richer F, Rouleau I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 1993;15:330–41.
[22] Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 2003;61:87–92.
[23] Lau EY, Eskes GA, Morrison DL, Rajda M, Spurr KF. Executive function in patients with obstructive sleep apnea treated with continuous positive airway pressure. J Int Neuropsychol Soc 2010;16:1077–88.
[24] Naegele B, Pepin JL, Levy P, Bonnet C, Pellat J, Feuerstein C. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 1998;21:392–7.
[25] Heinzer R, Gaudreau H, Décary A, Sforza E, Petit D, Morisson F, et al. Slow-wave activity in sleep apnea patients before and after continuous positive airway pressure treatment: contribution to daytime sleepiness. Chest 2001;119: 1807–13.
[26] Morisson F, Décary A, Petit D, Lavigne G, Malo J, Montplaisir J. Daytime sleepiness and EEG spectral analysis in apneic patients before and after treatment with continuous positive airway pressure. Chest 2001;119: 45–52.
[27] Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep 2007;30:711–9.
[28] Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. Respirology 2013;18:61–70.
[29] Aloia MS, Arnedt TJ, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: A critical review. J Int Neuropsychol Soc 2004;10:772–85.
[30] Bédard MA, Montplaisir J, Richer F, Malo J. Nocturnal hypoxemia as a determinant of vigilance impairment in sleep apnea syndrome. Chest 1991;100:367–70.
[31] Décary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. Sleep 2000;23:369–81.
[32] Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. Sleep 1987;10:254–62.
[33] Mathieu A, Mazza S, Décary A, Massicotte-Marquez J, Petit D, Gosselin N, et al. Effects of obstructive sleep apnea on cognitive function: A comparison between younger and older OSAS patients. Sleep Med 2008;9:112–20.
[34] Rouleau I, Décary A, Chicoine AJ, Montplaisir J. Procedural skill learning in obstructive sleep apnea syndrome. Sleep 2002;25:401–11.
[35] Salorio CF, White DA, Piccirillo J, Duntley SP, Uhles ML. Learning, memory, and executive control in individuals with obstructive sleep apnea syndrome. J Clin Exp Neuropsychol 2002;24:93–100.
[36] Verstraeten E, Cluydts R. Executive control of attention in sleep apnea patients: theoretical concepts and methodological considerations. Sleep Med Rev 2004;8:257–67.
[37] Verstraeten E, Cluydts R, Pevernagie D, Hoffmann G. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. Sleep 2004;27:685–93.
[38] Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev 2006;16:17–42.
[39] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11:1–16.
[40] Lezak M, Howieson D, Loring D. Neuropsychological assessment, fourth edition, Oxford University Press; 2004.
[41] Mazza S, Pépin JL, Naëgelé B, Plante J, Deschaux C, Lévy P. Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. Eur Respir J 2005;25:75–80.
[42] Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. Sleep 2013;36:1297–305.
[43] Sforza E, Haba-Rubio J, De Bilbao F, Rochat T, Ibanez V. Performance vigilance task and sleepiness in patients with sleep-disordered breathing. Eur Respir J 2004;24:279–85.
[44] Sphirer I, Elizur A, Shorer R, Peretz RB, Rabey JM, Khaigrekht M, et al. Hypoxemia correlates with attentional dysfunction in patients with obstructive sleep apnea. Sleep Breath 2012;16:821–7.
[45] Tulek B, Atalay NB, Kanat F, Suerdem M. Attentional control is partially impaired in obstructive sleep apnoea syndrome. J Sleep Res 2013;22:1–8.
[46] Kilpinen R, Saunamäki T, Jehkonen M. Information processing speed in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2014;129: 209–18.
[47] Aloia MS, Ilniczky N, Di Dio P, Perlis ML, Greenblatt DW, Giles DE. Neuropsychological changes and treatment compliance in older adults with sleep apnea. J Psychosom Res 2003;54:71–6.
[48] Saunamäki T, Jehkonen M. A review of executive functions in obstructive sleep apnea syndrome. Acta Neurol Scand 2007;115:1–11.
[49] Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65–94.

[50] Naëgelé B, Thouvard V, Pépin JL, Lévy P, Bonnet C, Perret JE, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;18:43–52.
[51] Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial difference in sleep disordered breathing in African Americans and Caucasians. Am J Respir Crit Care Med 1997;155:186–92.
[52] Miyake A, Shah P. Models of working memory: mechanisms of active maintenance and executive control. United Kingdom: Cambridge University Press; 1999.
[53] Aloia MS, Ilniczki N, Di Dio P, Perlis ML, Greenblatt DW, Giles DE. Neuropsychological changes and treatment compliance in older adults with sleep apnea. J Psychosom Res 2003;54:71–6.
[54] Tulving E, editor. Episodic and semantic memory in organisation of memory, New York: Academic Press; 1972.
[55] Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. Sleep 2013;36:203–20.
[56] Kloepfer C, Riemann D, Nofzinger EA, Feige B, Unterrainer J, O'Hara R, et al. Memory before and after sleep in patients with moderate obstructive sleep apnea. J Clin Sleep Med 2009;5:540–8.
[57] Twigg GL, Papaioannou I, Jackson M, Ghiassi R, Shaikh Z, Jaye J, et al. Obstructive sleep apnea syndrome is associated with deficits in verbal but not visual memory. Am J Respir Crit Care Med 2010;182:98–103.
[58] Djolagic L, Guo M, Matteis P, Carusona A, Stickgold R, Malhotra A. Untreated sleep-disordered breathing: links to aging-related decline in sleep-dependant memory consolidation. PLoS One 2014;29:1–7.
[59] Zhang Q, Wang D, Qin W, Li Q, Chen B, Zhang Y, et al. Altered resting-state brain activity in obstructive sleep apnea. Sleep 2013;1:651–9.
[60] Diekelmann S, Biggel S, Rash B, Born J. Offline consolidation of memory varies with time in slow wave sleep and can be accelerated by cuing memory reactivations. Neurobiol Learn Mem 2012;98:103–11.
[61] Quan SF, Chan CS, Dement WC, Gevins A, Goodwin JL, Gottlieb DJ, et al. The association between obstructive sleep apnea and neurocognitive performance–The apnea positive pressure long-term efficacy study (APPLES). Sleep 2011;34:303–14.
[62] Lee MM, Strauss ME, Adams N, Redline S. Executive functions in persons with sleep apnea. Sleep Breath 1999;3:13–6.
[63] Panossian LA, Veasey SC. Daytime sleepiness in obesity: mechanisms beyond obstructive sleep apnea - a review. Sleep 2012;35:605–15.
[64] Feng J, Wu Q, Zhang D, Chen BY. Hippocampal impairments are associated with intermittent hypoxia of obstructive sleep apnea. Chin Med J 2012;125:696–701.
[65] Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest 2012;141:1601–10.
[66] Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med 2011;183:1419–26.
[67] Gozal D, Danial JM, Dohanich GP. Behavioural and anatomical correlates of chronic episodic hypoxea during sleep rat. J Neurol Sci 2001;21:2442–50.
[68] McCoy JG, McKenna JT, Connolly NP, Poca DL, Ling L, McCartey RW, et al. One week of exposure to intermittent hypoxia impairs attentional set-shifting in rats. Behav Brain Res 2010;210:123–6.
[69] Kielb SA, Ancoli-Israel S, Rebok GW, Spira AP. Cognition in obstructive sleep apnea-hypopnea syndrome (OSAS): current clinical knowledge and the impact of treatment. Neuromolecular Med 2012;14:180–93.
[70] Gagnon K, Baril AA, Décary A, Lafond C, Gagnon JF, Gosselin N. Mild cognitive impairment in obstructive sleep apnea [abstract]. In: World Association of Sleep Medicine Congress. 2013. p. 145 [Available from: URL: http://www.wasmcongress.com/wp-content/uploads/2012/03/WASM-2013-Abstracts-Publication.pdf].
[71] Alchanatis M, Zias N, Deligiorgis N, Liappas I, Chroneou A, Soldatos C, et al. Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. Sleep Breath 2008;12:17–24.
[72] Alchanatis M, Zias N, Deligiorgis N, Amfilochiou A, Dionellis G, Orphanidou D. Sleep apnea-related cognitive deficits and intelligence: an implication of cognitive reserve theory. J Sleep Res 2005;14:69–75.
[73] Cosentino FI, Bosco P, Drago V, Prestianni G, Lanuzza B, Iero I, et al. The APOE ε4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. Sleep Med 2008;9:831–9.
[74] Nikodemova M, Finn L, Mignot E, Salzieder N, Peppard PE. Association of sleep disordered breathing and cognitive deficit in APOE ε4 carriers. Sleep 2013;36:873–80.
[75] Mathieu A, Mazza S, Petit D, Décary A, Massicotte-Marquez J, Malo J, et al. Does age worsen EEG slowing and attention deficits in obstructive sleep apnea syndrome? Clin Neurophysiol 2007;118:1538–44.
[76] Morisson F, Lavigne G, Petit D, Nielsen T, Malo J, Montplaisir J. Spectral analysis of wakefulness and REM sleep EEG in patients with sleep apnoea syndrome. Eur Respir J 1998;11:1135–40.
[77] Xiromeritis AG, Hatziefthimiou AA, Hadjigeorgiou GM, Gourgoulianis KI, Anagnostopoulou DN, Angelopoulos NV. Quantitative spectral analysis of vigilance EEG in patients with obstructive sleep apnoea syndrome. Sleep Breath 2011;15:121–8.
[78] Lee SD, Ju G, Kim JW, Yoon IY. Improvement of EEG slowing in OSAS after CPAP treatment. J Psychosom Res 2012;72:126–31.
[79] Picton TW. The P300 wave of the human event-related potential. J Clin Neurophysiol 1992;9:456–79.
[80] Raggi A, Ferri R. Cognitive evoked potentials in obstructive sleep apnea syndrome: a review of the literature. Rev Neurosci 2012;23:311–23.
[81] Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry the P300 as a measure of stimulus evaluation time. Science 1997;197:792–5.
[82] McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency reaction time. Science 1981;211:77–80.
[83] Baril AA, Gagnon K, Gagnon JF, Montplaisir J, Gosselin N. Association between waking electroencephalography and cognitive event-related potentials in patients with obstructive sleep apnea. Sleep Med 2013;14:685–7.
[84] Gosselin N, Mathieu A, Mazza S, Décary A, Malo J, Montplaisir J. Deficits in involuntary attention switching in obstructive sleep apnea syndrome. Neurosci Lett 2006;408:73–8.
[85] Gosselin N, Mathieu A, Mazza S, Petit D, Malo J, Montplaisir J. Attentional deficits in patients with obstructive sleep apnea syndrome: an event-related potential study. Clin Neurophysiol 2006;117:2228–35.
[86] Rumback L, Krieger J, Kurtz D. Auditory event-related potential in obstructive sleep apnea: effects of treatment with nasal continuous positive airway pressure. Electroencephalogr Clin Neurophysiol 1991;80:454–7.
[87] Walsleben JA, O'Malley EB, Bonnet K, Norman RG, Rapoport DM. The utility of topographic EEG mapping in obstructive sleep apnea syndrome. Sleep 1993;16:S76–8.
[88] Kotterba S, Rasche K, Widdig W, Duscha C, Blombach S, Schultze-Werninghaus G, et al. Neuropsychological investigations and event-related potentials in obstructive sleep apnea syndrome before and during CPAP-therapy. J Neurol Sci 1998;159:45–50.
[89] Sangal RB, Sangal JM. Visual P300 latency in obstructive sleep apnea does not change acutely upon treatment with CPAP. Sleep 1997;20:702–4.
[90] Inoue Y, Nanba K, Kojima K, Mitani H, Arai AH. P300 abnormalities in patients with severe sleep apnea syndrome. Psychiatry Clin Neurosci 2001;55:247–8.
[91] Ferini-Strambi L, Marelli S, Galbiati A, Castronovo C. Effects of continuous positive airway pressure on cognition and neuroimaging data in sleep apnea. Int J Psychophysiol 2013;89:203–12.
[92] Torelli F, Moscufo N, Garreffa G, Placidi F, Romigi A, Zannino S, et al. Cognitive profile and brain morphological changes in obstructive sleep apnea. NeuroImage 2011;54:787–93.
[93] Kumar R, Chavez AS, Macey PM, Woo MA, Yan-Go FL, Harper RM. Altered global and regional brain mean diffusivity in patients with obstructive sleep apnea. J Neurosci Res 2012;90:2043–52.
[94] Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM. Brain structural changes in obstructive sleep apnea. Sleep 2008;31:967–77.
[95] Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. J Appl Physiol 2005;98:2226–34.
[96] Castronovo V, Canessa N, Strambi LF, Aloia MS, Consonni M, Marelli S, et al. Brain activation changes before and after PAP treatment in obstructive sleep apnea. Sleep 2009;32:1161–72.
[97] Ayalon L, Ancoli-Israel S, Klemfuss Z, Shalauta MD, Drummond SP. Increased brain activation during verbal learning in obstructive sleep apnea. Neuroimage 2006;31:1817–25.
[98] Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306:613–9.